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09/824,358	04/02/2001	Michael R. Green	07917-083002/UMMC 99-10	9355

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/824,358	Applicant(s) GREEN ET AL.	
	Examiner Anne Baker	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Claims 1-17 are pending in the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 13-15 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a transgenic cell which reads on an *in vivo* human cell, which is non-statutory subject matter. Use of the phrase "isolated transgenic cell" or "nonhuman" would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the full scope of the claimed invention. Applicants are referred to the interim guidelines on written description published June

15, 1998 in the Federal Register at Volume 63, Number 114, pp. 32639-32645 (also available at www.uspto.gov).

Claims 12-16 are drawn to a gene or transgenic cell comprising an aptamer sequence incorporated into the 5' UTR-encoding region of a gene. However, the specification only discloses aptamers that bind to a few cell-permeable small molecules, such as tobramycin, kanamycin, and Hoeschst dyes. There are millions of molecules that are cell-permeable and less than 1000 Da. However, the specification does not disclose aptamers that bind to a representative number of small molecules. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, only aptamers that bind to aminoglycoside antibiotics and Hoeschst dyes are disclosed. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, although methodology exists to select for aptamers that bind small molecules the specification does not disclose any aptamers beyond the few exemplified. This limited information regarding the contemplated embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the full scope of aptamers suitable for use in the method of repressing translation at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to provide an enabling disclosure for the method for controlling expression of a gene because the specification does not teach how to use the method in any application. Claims 1-11 are directed to a method for controlling the expression of a gene in a living cell, wherein an aptamer that binds specifically to a cell-permeable small molecule is incorporated into the 5' UTR-encoding region of a gene. The specification reveals that the incorporation of the aptamer will specifically inhibit translation of the linked gene (p. 2, lines 25-28). The specification contemplates that the claimed method can be used in gene therapy applications (p. 3, lines 1-2), target validation studies (p. 3, lines 20-21 and pp. 13-14), or to make transgenic yeast, transgenic plants, or transgenic animals (p. 8, line 23 to p. 9, line 17). However, methods of gene therapy are not routinely successful, as discussed below, and the specification does not adequately disclose how to perform target validation studies using the claimed method. Furthermore, the specification does not teach how to use the claimed method in transgenic organisms.

The specification does not teach how to use the claimed methods and compositions for target validation. Claim 12 is directed to a gene comprising an aptamer sequence incorporated into the 5' UTR-encoding region of a gene. Claims 13-15 are directed to a transgenic cell comprising an aptamer incorporated into the 5' UTR-encoding region of a gene. Claim 16 is directed to a bacterial resistance marker comprising an aptamer sequence operably linked to a bacterial expression control sequence. The specification does not adequately teach how to use any of the claimed compositions for target validation studies because no guidance is offered with regard to how one skilled in the art would knockout an essential gene in any microbial cell or any animal cell and simultaneously introduce a transgene of the type recited in the claims such that the essential nature of the gene of interest could then be evaluated by contacting the cell with the cell-permeable small molecule, thereby inhibiting translation of the gene of

interest from the transgene construct. The specification suggests that known techniques of gene targeting, i.e. homologous recombination can be used to incorporate an aptamer into an endogenous gene (p. 8, lines 23-30). However, the specification does not teach how to perform such methods in a microbial pathogen or any other prokaryotic or eukaryotic cell (for target validation studies) or in the somatic cells of an animal (for gene therapy). Thus, the specification does not adequately teach how to use the claimed methods and compositions for target validation studies.

The specification fails to provide an enabling disclosure for the claimed target validation method because the specification does not teach how to transfect dead cells. Claim 17 is directed to a method for determining whether a gene of interest is essential for the survival or growth of a cell. The specification teaches that target validation can be used to identify a gene of a microbial pathogen that is essential for its survival, thus providing a target for drug therapy (p. 13, line 31 to p. 14, line 5). The first step of the method requires deletion of an endogenous gene of interest in the cell. The claimed method is not enabled because one of skill in the art would expect that the deletion of an essential gene would, by definition, lead to cell death before the subsequent steps of the method can be carried out. The subsequent steps involve incorporating an aptamer into the 5' UTR-encoding region of the gene of interest *in vitro* and introducing the altered gene into the cell. One of skill in the art would not expect to be able to introduce any gene into a dead cell.

The specification fails to provide an enabling disclosure for the claimed aptamer-linked bacterial resistance marker gene (Claim 16) because no guidance is offered with regard to how to use the claimed composition. The specification teaches that the instant invention can be used for gene therapy or target

validation studies. However, the specification does not teach how the claimed aptamer-linked bacterial resistance marker gene can be used in either application.

Claims 9 and 10 are specifically drawn to *in vivo* uses of the claimed method. Claims 1-8 encompass *in vivo* uses of the claimed method. The specification contemplates using the compositions of claims 12-15 in gene therapy applications. As discussed above, the specification contemplates that the claimed method can be used in gene therapy applications (p. 3, lines 1-2 and p. 9, lines 17-21), but the specification does not teach how to use the claimed methods in gene therapy applications. The specification fails to teach any method for transferring any gene into a target cell and expressing that gene at a therapeutic level in a diseased animal. The specification fails to provide an enabling disclosure for the use of the claimed methods in gene therapy applications because the specification does not offer any guidance in this regard and because methods of gene therapy are not routinely successful. Therefore, the disclosure must teach how to use the claimed methods with specific guidance. However, the specification does not provide any guidance as to the use of the claimed methods to treat a diseased animal. The specification does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the gene therapy vector required, for treatment of any pathological condition. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and

Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed methods for *in vivo* or *ex vivo* gene therapy. Thus, absent any showing that the claimed methods can be used in gene therapy applications to produce the intended therapeutic effect, the claims directed to methods for gene therapy are not enabled by the disclosure.

The specification fails to provide an enabling disclosure for the use of the claimed method and compositions in transgenic organisms. The specification contemplates that an aptamer-linked gene can be introduced into an animal by known techniques of gene targeting (p. 8, lines 24-30). However, homologous recombination techniques require a selection step to identify rare homologous recombinant embryonic stem cells that can then be injected into the blastocyst to create a chimeric mouse. This selection step typically relies on the incorporation of a drug resistance gene that will facilitate *in vitro* selection of homologous recombinants. The instant specification does not teach how transgenic organisms of any kind can be made using a construct of the type recited in the claims such that homologous recombinants can be identified and used to make the transgenic organism. Even if methods of random incorporation of an aptamer-linked transgene were used to generate a transgenic organism, undue experimentation would have been required to generate a useful transgenic organism because the

phenotype of a transgenic organism cannot be predicted. No guidance is provided with regard to how one would have prepared any transgenic organism. Expression of a transgene and the effect of transgene expression on the phenotype of the transgenic organism depends on the particular gene construct used, to an unpredictable extent. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). Furthermore, the operability of the claimed method *in vivo* (in animals, plants, or yeast) depends on a number of factors. Good et al. (1997) disclose that effective intracellular expression of small RNA therapeutics, whether antisense, ribozyme, or RNA aptamer, requires that the RNA be efficiently transcribed, stabilized against rapid degradation, folded correctly, and directed to the part of the cell where it can be most effective. The specification only teaches how to use the claimed method *in vitro* or in bacterial cells *in vivo*. Although the specification frequently refers to the experiments performed in cultured CHO cells as being "*in vivo*" (see, e.g., p. 6, lines 14-23 and p. 19, line 23 to p. 20, line 14), the experiments were actually performed *in vitro*. Use of the term "*in vivo*" to describe experiments performed in cell culture is contrary to the ordinary use of the term in the art. Thus the specification does not adequately teach how to use the claimed method in transgenic organisms. Given the lack of guidance and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to use the claimed methods and compositions in transgenic organisms.

The specification fails to provide an enabling disclosure for the claimed method of "controlling" the expression of a gene because the specification only teaches how to inhibit translation of a gene (see, e.g., p. 2, lines 25-28). The specification does not teach any other means of "controlling" expression of a gene. For example the specification does not teach how to use the instant invention to induce expression of a gene or increase basal levels of expression. "Controlling" expression of a gene implies that a

mechanism to both "turn on" and "turn off" the gene is provided. However, the instant specification only teaches how to use the method to repress gene expression.

The specification fails to provide an enabling disclosure for the method of Claim 1 because the specification does not offer any guidance for a method of controlling the expression of a gene in the absence of an aptamer incorporated into the 5' UTR-encoding region of the gene. Claim 1 is directed to a method for controlling the expression of a gene in a living cell, comprising contacting the 5' UTR of an RNA in the cell with a cell permeable small molecule. The specification does not teach how contacting the native 5' UTR of any RNA with any cell permeable small molecule can "control" expression of the gene.

Given the lack of working examples, the limited guidance in the specification, the broad scope of the claims, and the unpredictability of using the claimed methods in any application, undue experimentation would have been required for one skilled in the art to practice the claimed invention and to make and use the claimed compositions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is indefinite in its recitation of "a bacterial resistance marker" because it is unclear what this is. If the claim is intended to be directed to a drug resistance marker gene, clarifying claim language

would be remedial. Furthermore, a "marker" generally refers to a protein such as β-galactosidase and not the gene, but the specification does not teach how a protein could comprise an RNA aptamer.

Claim 17 is indefinite because it appears that the first step, wherein an essential endogenous gene candidate is deleted, potentially results in cell death (when the deleted gene is indeed essential) and thus it is unclear how any of the subsequent steps could be carried out on a dead cell.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step for evaluating whether the gene of interest is essential for survival or growth of the cell. The method is incomplete because after the cell is contacted with the cell-permeable small molecule, the cell is not observed for any particular effect resulting from contact with the molecule.

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER